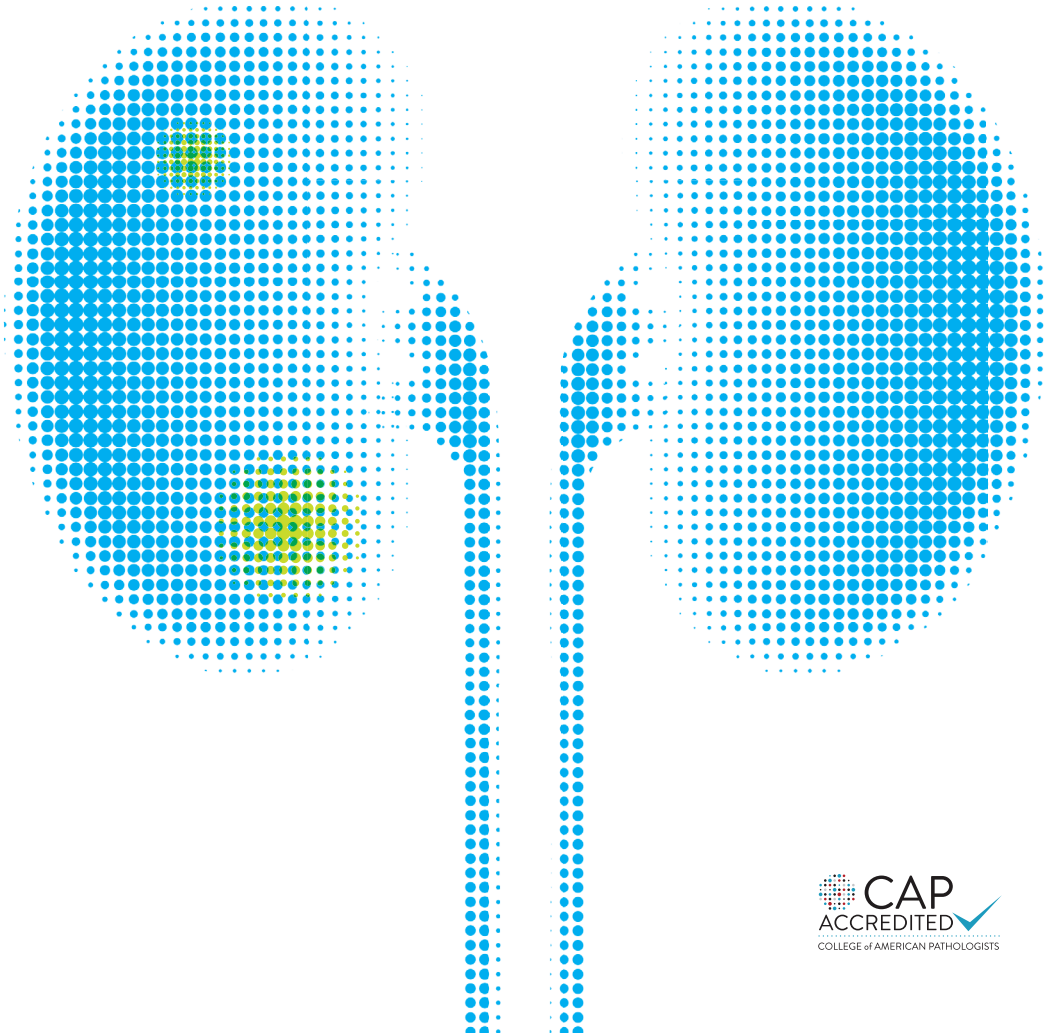
ACTIA
Inherited Genetics

MEDGENOME

Nephro Genetics



CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

Actia

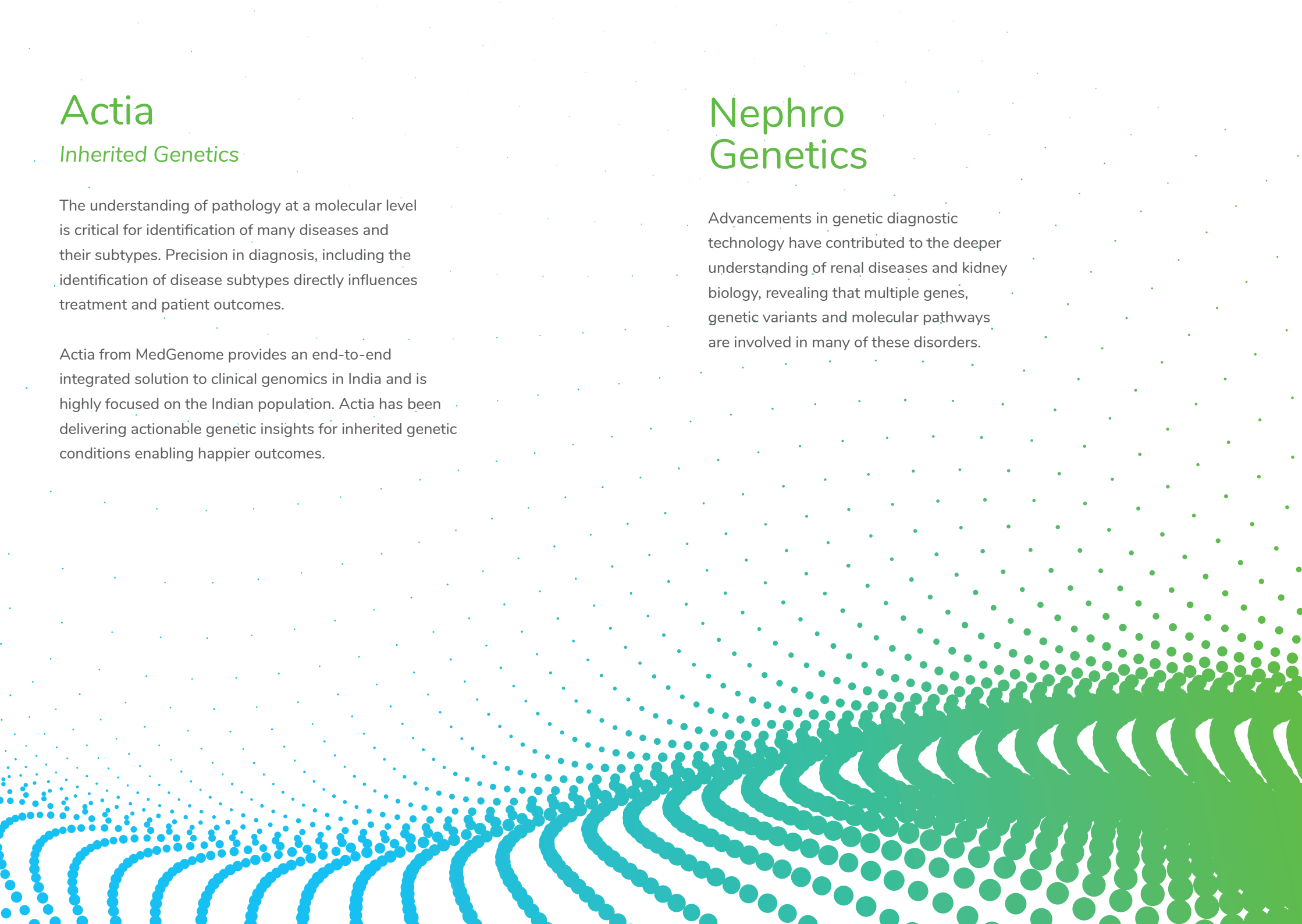
Inherited Genetics

The understanding of pathology at a molecular level is critical for identification of many diseases and their subtypes. Precision in diagnosis, including the identification of disease subtypes directly influences treatment and patient outcomes.

Actia from MedGenome provides an end-to-end integrated solution to clinical genomics in India and is highly focused on the Indian population. Actia has been delivering actionable genetic insights for inherited genetic conditions enabling happier outcomes.

Nephro Genetics

Advancements in genetic diagnostic technology have contributed to the deeper understanding of renal diseases and kidney biology, revealing that multiple genes, genetic variants and molecular pathways are involved in many of these disorders.



Renal disorders in children

- Genetic etiology comprises of a significant proportion of renal disease in childhood, and genome sequencing has helped identify numerous single-gene causes of early-onset of kidney disease.*
- These can be relatively common to rare disorders, from benign to those with a high morbidity and mortality.

Renal disorders in adults

- Several genetic disorders can be present in adult patients with renal insufficiency.
- Genetic renal disease other than Autosomal Dominant Polycystic Kidney Disease (ADPKD) accounts for End Stage Renal Disease (ESRD) in the adult population and molecular genetics can be of aid in the diagnostic process.

Prevalence of Genetic Renal Disorders (GRD)

- GRD affects 5-15% of the adult population.
- Renal diseases are influenced not only by the environment but also, genetic factors. [1]
- The prevalence of renal disease in children, including those with a GFR of <30 ml min/1.73 M^2 to ESRD, ranges from 21 to 55 per million age representative population.
- In countries with high rates of consanguinity and potentially greater risks of autosomal ESRD are reported as having hereditary renal disease. [3]
- 20% of cases of CKD are thought to be due to genetic forms of renal disease. [2]

What are the common Genetic Renal Disorders?

Renal Cystic & Interstitial Diseases

The cystic kidney diseases are also known as renal cystic ciliopathies.

Some of these are:

- Autosomal Dominant Polycystic Kidney Disease (ADPKD)
- Autosomal Recessive Polycystic Kidney Disease (ARPKD)
- Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)
- Nephronophthisis

Renal Tubular Disease

The following are classified under genetic renal tubular disorders:

- Bartter Syndrome
- Gitelman Syndrome
- Pseudohypoaldosteronism
- dRTA

Renal Glomerular Disorders

Some genetic glomerular diseases are:

- Steroid-Resistant Nephrotic Syndrome (SRNS)
- Familial Atypical HUS
- Alport Syndrome
- Fibronectin Glomerulopathy

*Fletcher, J., McDonald, S., Alexander, S.I. et al. Pediatr Nephrol (2013) 28: 251-256.
[1] Gluba-Brzózka A, Franczyk B, Olszewski R, et al. Int J Mol Sci. 2017 Jun 10;18(6).
[2] Mallett A, Patel C, Salisbury A, et al. Orphanet Journal of Rare Diseases. 2014;9:98.
[3] Fletcher, J., McDonald, S., Alexander, S.I. et al. Pediatr Nephrol (2013) 28: 251.

Nephrolithiasis

The heritability of renal stone formation (nephrolithiasis) has long been recognized. The advent of the genomic era has greatly increased the potential to define its underlying genetic defects. The following are the diseases:

- Primary Hyperoxaluria
- Cystinuria
- Hereditary Xanthinuri
- Dent Disease

Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT)

CAKUT account for approximately 50% of children with end-stage kidney disease. They occur in about 3 to 6 per 1,000 live births and constitute 20–30% of all anomalies identified in the neonatal period. They may present as an isolated feature or as part of clinical syndromes. Single-gene mutations in many different genes may cause a wide phenotypic spectrum of CAKUT and these are listed below:

- Renal Agenesis (RA)
- Renal Hypodysplasia (RHD)
- Multicystic Renal Dysplasia (MRD)
- Vesicoureteral Reflux (VUR 2)

Why test patients for Genetic Renal Disorders?

Highly penetrant mutations cause a wide range of renal phenotypes including:

- Diseases of renal growth (eg. Polycystic Kidney Disease)
- Diseases of abnormal glomerular function (eg. Congenital Nephrotic Syndrome)
- Abnormalities of blood pressure and electrolyte homeostasis (eg. Bartter Syndrome)

Correct diagnosis of GRD:

- Leads to specific investigations
- Can optimise treatment regimens
- Provides socio-economic benefits to the individual and family

Examples:

(i) aHUS genetic testing and its implication in management:

The diagnosis of genetic aHUS is established in a proband upon identification of a pathogenic variant(s) in one or more of the genes known to be associated with genetic aHUS which include C3, CD46 , CFB, CFH, CFHR1, CFHR3, CFHR4, CFI, DGKE, and THBD.

Eculizumab (a human anti-C5 monoclonal antibody) has been shown to induce remission of acute episodes of aHUS refractory to plasma therapy and is now widely used as a first-line therapy to treat aHUS, since this treatment has the potential to rescue renal functions when administered early. Eculizumab therapy may not be beneficial to those with aHUS caused by pathogenic variants in DGKE

An important advancement has been the development of transplant protocols integrating Eculizumab treatment to treat post-transplantation aHUS recurrence, as reported in individuals with pathogenic variants in C3, CFH, and CFI. Eculizumab prophylactic therapy may also prevent post-transplantation aHUS recurrence

Source: Mallett A, et al. Genomics in the renal clinic - translating nephrogenetics for clinical practice. Hum Gen. 2015 Jun 24;9:13.

(ii) Renal transplant in aHUS

Renal transplantation may be an option, although recurrence of disease in the graft limits its usefulness. Evidence suggests that kidney graft outcome is favorable in those with CD46 and DGKE pathogenic variants but not in those with C3, CFB, CFH, CFI, or THBD pathogenic variants.

Precipitation of aHUS in previously healthy donors has been reported. Molecular genetic studies revealed that one of the donors had a CFH pathogenic variant that put him at risk for aHUS. Thus, molecular genetic testing is recommended before live related donation to avoid the risk of triggering disease in the donor.

(iii) The Role of Uromodulin (UMOD) in Hypertension and Chronic Kidney Disease

Mutations in UMOD, which encodes Uromodulin, are associated with Medullary Cystic Kidney Disease Type 2, a rare dominantly inherited cause of CKD. Recent Genome Wide Association Studies (GWAS) studies have identified susceptibility variants for chronic kidney disease and hypertension in UMOD. Risk variants in UMOD directly increase UMOD expression, leading to salt-sensitive hypertension, secondary to activation of the renal sodium- potassium-chloride cotransporter NKCC2. Uromodulin may be a novel therapeutic target to control blood pressure and preserve renal function.

When to get tested for Genetic Renal Disorders?

Genetic testing for renal diseases can be done when an individual presents with:

- *Lower abdominal/loin pain*
- *Urinary tract infections*
- *Hematuria*
- *Renal dysfunction*
- *Family history of kidney disease*

Who needs to be tested for Genetic Renal Disorders ?

- Individuals presenting with the symptoms of a kidney disorder
- Individuals with a standard preliminary test showing the possibility of kidney disorder
- Individuals with a family history of kidney disorder
- Individuals without a family history but if any individuals in the family with symptoms resembling a specific disease condition
- Pre-natal testing is recommended only in families with affected individuals

Why recommend Actia for patients with Genetic Renal Disorders?

With an in-depth disease understanding and incorporating the latest research into the particular genetic disorder, Actia has developed a broad range of pre-designed gene mutation panels.

- *Polycystic Kidney Disease gene panel (ARPKD: PKHD1/ADPKD: PKD1 & PKD2)*
- *Meckel Gruber Syndrome gene panel*
- *VHL gene analysis*
- *Von Hippel-Lindau Syndrome (VHL) deletion/duplication analysis*
- *Joubert Syndrome gene panel*
- *Bardet-Biedl Syndrome gene panel*
- *TSC1 & TSC2 gene analysis*
- *Bartter syndrome gene panel*
- *Nephrotic Syndrome gene pane*
- *Hemolytic Uremic Syndrome - HUS (CFH, CFHR1 & CFHR3) deletion duplication analysis*
- *Primary Hyperoxaluria gene panel*
- *Homocystinuria gene panel*
- *Clinical Exome*

Test methodology

Next Generation Sequencing (NGS)

Using genomic DNA extracted from blood, the coding regions of all the genes are captured and sequenced simultaneously by NGS technology on an Illumina platform. The sequence data that is generated is aligned and analyzed for sequence variants.

Multiplex Ligation-dependent Probe Amplification (MLPA)

Deletion and duplication analysis of genomic DNA is carried out by MLPA. This method allows for the amplification of multiple targets with only a single primer pair.

Test sample requirements

Blood (3-5ml in EDTA tubes)

or

Extracted DNA samples
(1µg high quality DNA)

Required forms

- Relevant clinical information including all the clinical presentations and symptoms
- Test request form

Turnaround time

The time taken for generating a clinical report will be maximum of

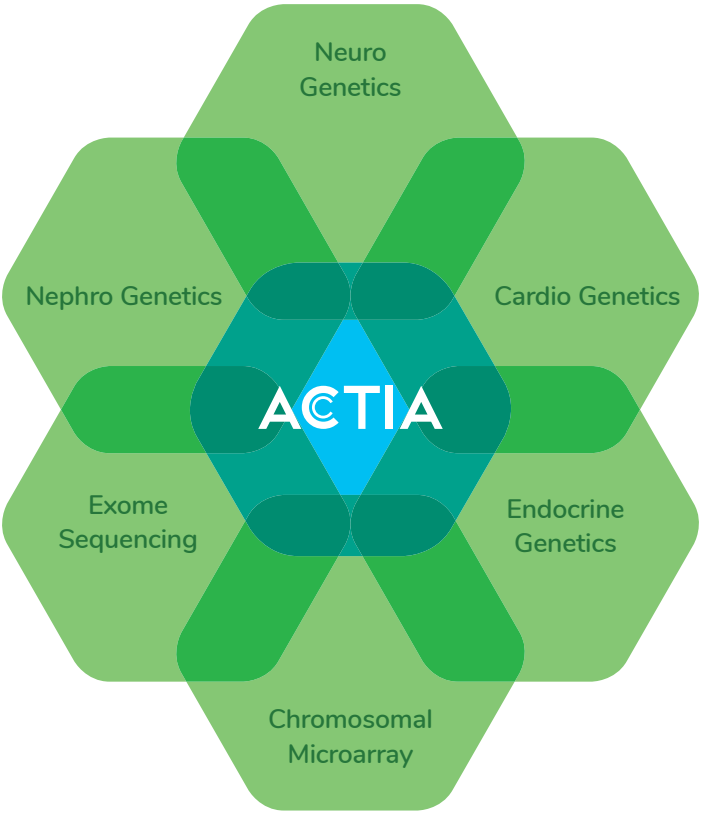
- 6 weeks for NGS
- 3 weeks for MLPA
- 3 weeks for Sanger Sequencing

Free genetic counselling

Actia offers all your patients FREE pre & post test genetic counselling with our expert and certified genetic counsellors.

Best available support for your patients and families via

- Latest technologies
- Helpful customer service
- Clear result interpretation
- Counselling sessions with our Genetic Counsellors



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